Systemic Lupus Erythematosus

The Effect of Corticotropin and Adrenocorticoid Therapy on Survival Rate

JACK POSNICK, *M.D.*, San Francisco

• **Ninety-four cases of systemic lupus erythematosus (SLE) were reviewed to assess the effect of adrenocorticotropin and adrenocorticoids on survival rate. Of the 43 patients who died, the mean survival in treated cases was 4.7 years, compared with 2 years in the control group. Utilizing a modified life table method, five-year survival rates were calculated for patients with SLE classified according to the severity of symptoms at the onset of disease. Survival rates for the treated and control groups were similar for patients with *mild* SLE, but definitely favored the treated patients who had *moderate* or *severe* forms of the disease. Thus, corticotropin or adrenocorticoid therapy seems definitely indicated in the *moderate* and certainly in the *severe* cases of SLE.**

THE INITIAL REPORT by Hench and coworkers,[9] concerning the use of pituitary adrenocorticotropic hormone and cortisone in the treatment of rheumatoid arthritis, heralded a wave of enthusiasm for what appeared to be a major advancement toward the eradication of a host of disorders. The medical literature soon became replete with reports concerning the dangers and limitations of these drugs and it rapidly became apparent that the symptomatic benefits observed were difficult to sustain with safe maintenance dosages. In addition, it was demonstrated convincingly that this therapy seldom altered the ultimate course of the two most common chronic inflammatory diseases, rheumatoid arthritis[1,14,18] and rheumatic fever.[26] Yet there has been general agreement that adrenocorticoids may be lifesaving in certain fulminating conditions such as anaphylactic shock, status asthmaticus, pemphigus, overwhelming infection and acute systemic lupus erythematosus (SLE).* In clinics dealing with large numbers of cases of systemic lupus erythematosus there have been indications that the life history of this particular collagen disease may be favorably affected with regard to both morbidity and mortality.†

This study concerns 94 cases of SLE treated at the University of California Medical Center from 1940 through 1960 and endeavors to appraise the effect of corticotropin and adrenocorticoid therapy on survival rates.

METHOD OF STUDY

The data reported in this evaluation were compiled from the medical records of patients proved to have SLE by autopsy, by biopsy or by the presence of lupus erythematosus cells on two or more occasions coincident with clinical symptoms of SLE.

Included in the control group were all patients in whom SLE began before 1950 (the approximate year that corticotropin and adrenocorticoids became generally available). Those patients within the control group who eventually received adrenocorticoid therapy were withdrawn from the study on the date they began treatment. The number of control patients totalled 39.

The treated group consisted of every patient in whom the disease began in 1950 or later. There were 55 of them and all but six received adrenocorticoid therapy. In analyzing the data it became apparent that it would not be practical to consider in detail the type of adrenocorticoid or corticotropin therapy the patients received, as the preparations used were quite varied and doses were changed frequently during the course of the disease. Suffice it to say that the treated patients invariably received as a minimum daily maintenance dose the equivalent of 30 mg of hydrocortisone and, more often, doses of both corticotropin and adrenocorticoids two or three times this amount. During acute exacerbations high doses were employed in nearly all cases.

Striving for the most reliable means of comparison, cases were classified as *mild*, *moderate* or *severe* by means of inspection of the histories and physical examinations reported in patient records but without knowledge of the ultimate course of the illness. The series was thus divided in order to correct for the larger proportion of more recent cases of SLE which were diagnosed sooner after onset and represented milder forms of the disease. The factor of earlier recognition of the disease after 1950 would tend to make data from earlier periods not

*Reference Nos. 2, 8, 12, 13, 15, 16, 20-23, 25.

†Reference Nos. 2, 4, 6, 8, 10, 11, 15, 22-24.

From the Department of Medicine and the Metabolic Research Unit, University of California School of Medicine, San Francisco 22.

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comparable with those of later times unless some such classification is used. In addition it seemed more reliable to compare patients who had approximately the same degree of illness. The classification of *mild* was assigned to patients in whom the disease began with minimal complaints such as dermatitis or nondisabling arthropathy unaccompanied by objective joint signs. Patients with initial manifestations of extensive dermatitis, objective arthropathy resulting in partial restriction of activity, or both, were included in the *moderate* group. The *severe* group comprised patients with a history of rapid fulminating onset and complete incapacitation. Examples of the latter include those with rapid development of anasarca, pleural effusion, hemiplegia, seizure and decidedly elevated temperature with coma and overwhelming arthritis.

With these criteria, an attempt was made to assess the five-year survival rate by a modified life table method described by Cutler and Ederer[22] which permits inclusion of patients who came under observation less than five years before the closing date of the study.

RESULTS

Data on the sex, race and age at onset, presented in Table 1, closely approximate data from numerous large series previously reported.[6,7,11,24]

The onset was considered to be the time of the appearance of the first significant sign or symptom of SLE, determined as accurately as possible from medical records or personal interview. The age span was similar in both the control and treated patients, approximately 80 per cent falling within the age range of 10 to 40 years.

Polyarthropathy and dermatitis, as would be expected, were the most frequent presenting manifestations of the disease (Table 2), the former being the first sign of onset in 54.2 per cent of the patients and the latter in 25.5 per cent. Less common initial signs were: fever, 7.5 per cent; edema, 5.3 per cent; seizure, 1 case; pleural effusion, 1 case; hemoptysis, 1 case; and toe ulcer, 1 case.

Of all the patients observed, 43 died, 23 in the control group and 20 among the treated. The mean survival for all who died was 3.3 years. The mean survival for treated patients was 4.7 years as compared with 2 years in the control group.

Chart 1 presents the cumulative proportions surviving from the onset of disease to varying yearly intervals for the entire series as a whole as well as for the control and the treated groups. The probability of five-year survival for the treated cases was 73 per cent, compared with 49 per cent for the control group. When extending the life table to ten years, the survival figures on the basis of a statistically diminishing sample were 55 per cent and 33 per cent respectively, for the same groups. It may be noted that the survival curve drops most precipitously in the first two years, especially in the control series.

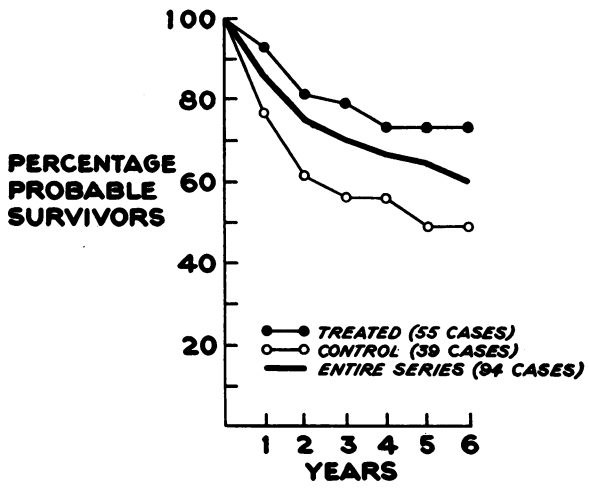

Chart 1.—Survival rates of patients with systemic lupus erythematosus treated with steroids compared with untreated patients.

TABLE 1.—*Data on Age at Onset, Sex and Race of 94 Patients with Systemic Lupus Erythematosus*

	Control	Treated	Total
Number cases	39	55	94
Age at onset, years	28.3	30.4	29.5
Females, per cent	77	74.5	75.75
Males, per cent	23	25.5	24.25
White, per cent	92.3	83.6	87.2
Negro, per cent	5.1	12.7	9.6
Oriental, per cent	2.6	3.7	3.2

TABLE 2.—*Initial Manifestations of Disease in 94 Cases of Systemic Lupus Erythematosus*

	Control	Treated	Total
Number cases	39	55	94
Polyarthropathy, per cent	41	63.6	54.2
Dermatitis, per cent	25.7	25.4	25.5
Fever, per cent	10.2	5.4	7.5
Edema, per cent	10.2	1.8	5.3
Other, per cent	12.9	3.7	7.5

Utilizing the same life table method, Chart 2 shows the probable survival curves as calculated for the three classifications of SLE (mild, moderate and severe, as previously described). It will be noted that the survival curves for the *mild* cases, treated and untreated, are nearly identical, as 75 per cent of the treated cases and 69 per cent of the control patients had survived at the end of five years. In considering the *moderate* cases, it is observed that a rather pronounced difference exists in survivorship by the end of the fifth year, as 87 per cent of the treated patients and 49 per cent of the controls were

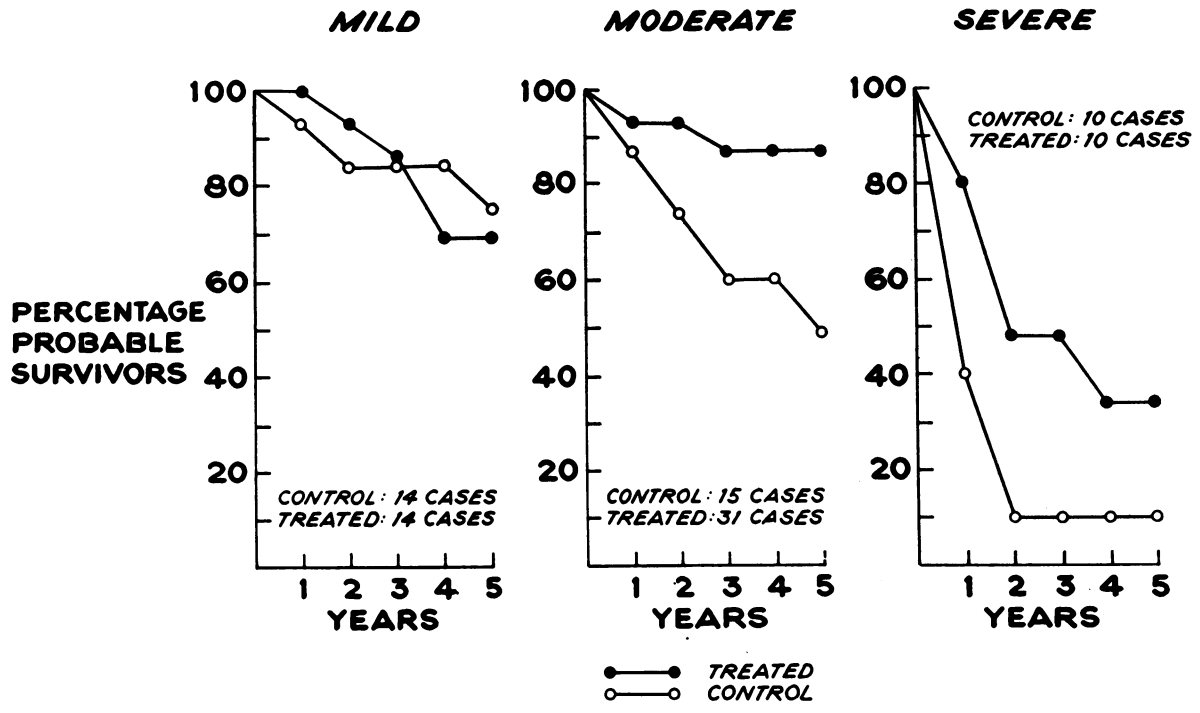

Chart 2.—Survival rates, according to severity of disease, of patients with steroid-treated and untreated systemic lupus erythematosus.

living at that time. The probability of survival among the *severe* cases was much less for both groups, especially during the first two years after onset. The five-year survival rates for this group were 34 per cent for treated cases and 10 per cent for the controls. All but two of the patients in the *severe* group had died by the end of the fifth year.

Autopsy was done in each of the 37 cases in which the patient died. Age at onset, sex and race were no different for those who died than for those remaining in the series. Table 3 shows the major causes of death, and the significant autopsy findings are summarized in Table 4.

It will be noted that in approximately 80 per cent of the cases in which the patient died the cause of death was definitely SLE, while the remainder died of intercurrent disease such as pneumonia (three cases), intracerebral hemorrhage (one case), staphylococcus septicemia (one case), and gastrointestinal hemorrhage (one case). While the major causes of death, for the series as a whole, were cardiac failure and uremia, a striking difference is noted between the treated and the control groups. Death in the control group was the result of cardiac failure in approximately half the patients whereas one-fourth died of uremia. The reverse was true in the treated patients. This would correlate somewhat with the higher incidence of Libman-Sacks endocarditis noted at autopsy in the control group but

TABLE 3.—*Cause of Death in 37 Cases of Systemic Lupus Erythematosus*

	Control	Treated	Total
Number autopsies	21	16	37
Cardiac failure, per cent	52.4	25.0	40.6
Uremia, per cent	23.8	56.2	37.9
Pneumonia, per cent	14.3	0	8.1
Other, per cent	9.5	18.8	13.4
SLE, per cent	80.9	81.3	81.1
Intercurrent disease, per cent	19.1	18.7	18.9

TABLE 4.—*Autopsy Findings in 37 Cases of Systemic Lupus Erythematosus*

	Control	Treated	Total
Libman-Sacks endocarditis, per cent	52.4	31.3	43.3
"Wire loop" kidneys, per cent	66.7	56.2	62.2
Serositis, per cent	71.4	62.2	67.6
Bacterial infection, per cent	61.9	62.2	62.2

bears no relationship to the pathology report of kidney "wire-loop" changes present in more than half of both groups. Lupus glomerular changes were noted in the treated cases with approximately 10 per cent less frequency than in the controls.

Bacterial infection was present in approximately 60 per cent of both groups of the autopsied cases and involved the lung in 19 cases, the kidney in three, and the blood stream in two. Tuberculosis, present in three patients in the series, was pulmonary in one living patient and miliary in one who is still

living and in another who died. All three were given adrenocorticoids before the diagnosis of tuberculosis was made.

DISCUSSION

In the many reported reviews of SLE, no investigator has attempted a detailed statistical evaluation of the effect of adrenocorticoids on survival rate in this disease. This is understandable in view of the many obstacles involved in dealing with a chronic variable disease. The establishment of a perfect concurrent untreated control series is not possible inasmuch as nearly every patient with SLE in recent years has received adrenocorticoid therapy. Nevertheless, it is felt that important information can be derived from a study such as this, which is presented more as a general prognostic survey than as infallible conclusions.

The results of this study suggest that SLE under present management is no longer a rapidly fatal disease. Recent reports of favorable survival time in SLE include patients who for the most part have received adrenocorticoid therapy. Rupe and coworkers[19] reported a survival time longer than ten years in more than half his series of 100 patients of whom all but seven received adrenocorticoids. Additional evidence of its long term benefits in the treatment of SLE is found in the series by Soffer and coworkers,[24] Haserick,[8] McCombs and Patterson,[15] Jalil and coworkers[10] and Dubois.[5]

While data from the entire series (Chart 1) indicates an appreciable difference between the survival time of the treated and the control groups, adrenocorticoid therapy is not strongly impressive as a truly effective medication. The life tables separating the series population according to type of onset, as in Figure 2, give more significant and more useful information, and tend to be more accurate for reasons listed in the method of study. Harvey and coworkers[7] reported a significant difference in survivorship in favor of cases with longer intervals between onset and diagnosis while those patients with serious symptoms at the onset appeared to have more rapid progression of disease. Their finding is paralleled in this study.

The nearly identical survival time of treated and control patients in the *mild* classification would indicate that adrenocorticoids are of little or no benefit in this particular group. Limiting therapy to rest and salicylates in mild cases of SLE, as recommended by Dubois,[5] would certainly be warranted. The rather noticeable difference in survival time in the group of *moderate* cases would support the use of adrenocorticoids for this group. Although every patient except two in the *severe* group died within five years of onset regardless of the form of therapy, the survival time did appear to favor the treated patients. There is no question that intensive adrenocorticoid therapy is justified in this group. Pollak and coworkers[17] have recommended prednisone in doses of 40 to 100 mg daily in order to effectively suppress all signs of disease activity.

A review of the autopsy data in Table 4 reveals very little difference between the treated and control patients who died, with the exception of the lower incidence of Libman-Sacks endocarditis among the patients who received treatment. Whether the anti-inflammatory effect of adrenocorticoid therapy was instrumental in reducing the frequency of verrucous vegetations is an interesting speculation. While more patients in the treated group apparently died of uremia, "wire-loop" kidney was found in 10 per cent more of the untreated cases. Of the nine patients treated with adrenocorticoids who died of uremia, seven began taking the steroid after abnormal renal findings were detected aand there was no evidence in the medical records that the use of them aggravated the renal disease. Pollak and coworkers,[17] in a study of 33 patients with renal lesions of SLE, reported that very high adrenocorticoid doses produced in many cases striking prolongation of life span and improvement of renal lesions.

Major bacterial infection was present post mortem in the same frequency among both the treated and control patients, thus absolving the adrenocorticoids of blame for the spread of infection in all instances.

It is concluded that this study verifies clinical impressions of recent years that corticotropin and adrenocorticoid therapy prolongs life in certain cases of SLE. Such treatment can by no means be considered the final answer in this perplexing disease, which will probably remain incurable until the pathogenesis is better understood.

Metabolic Research Unit, U. C. School of Medicine, San Francisco 22.

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